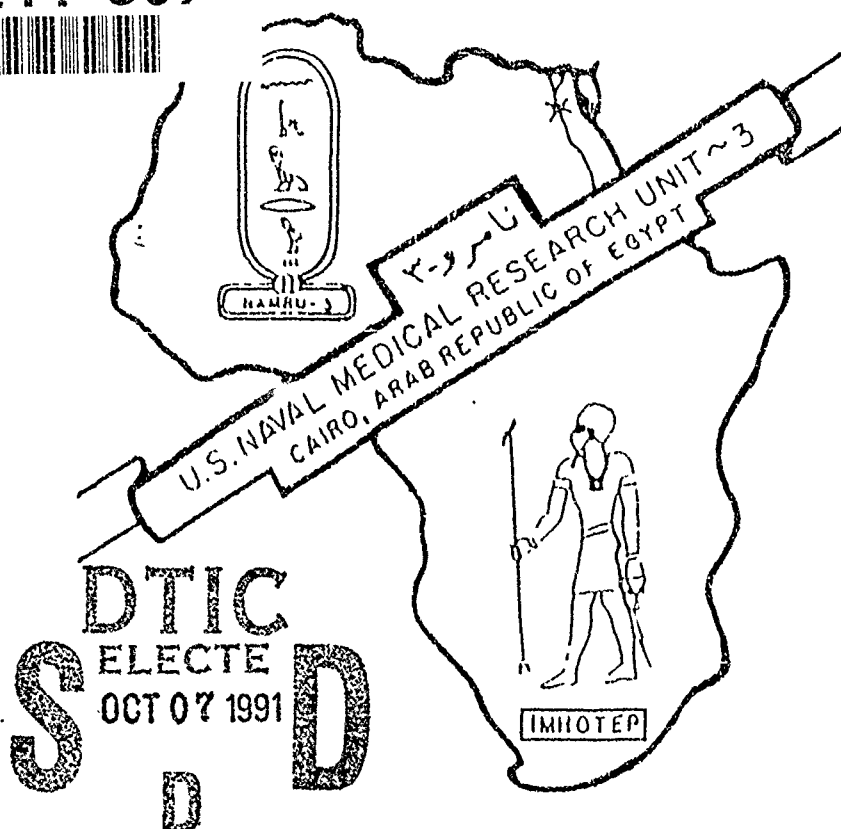




2



## PUBLICATION REPORT

This document has been approved  
for public release and sale; its  
distribution is unlimited.

1615

97/89-90

NORFLOXACIN FOR THE PROPHYLAXIS OF  
TRAVELERS' DIARRHEA IN U.S. MILITARY PERSONNEL

BY

Daniel A. Scott, Richard L. Haberberger,  
Scott A. Thornton and Kenneth C. Hyams

U.S. NAVAL MEDICAL RESEARCH UNIT NO. 3  
(CAIRO, ARAB REPUBLIC OF EGYPT)

FPO NEW YORK 09527

01 10 4 137

91-12593



TABLE 1  
Comparison of demographic factors between norfloxacin and placebo groups

Factor (mean $\pm$ SD)	Placebo (n = 117)	Norfloxacin (n = 105)	P value
Age	26.1 $\pm$ 6.9	26.5 $\pm$ 9.9	0.71
Days ashore	2.8 $\pm$ 0.9	2.9 $\pm$ 0.9	0.16
Days in Cairo	1.3 $\pm$ 0.7	1.4 $\pm$ 0.6	0.62
Days in Alexandria	1.4 $\pm$ 1.1	1.6 $\pm$ 1.2	0.35
No. completing study/No. enrolled	117/138	105/124	0.99
History of previous travel to Egypt	13/116	5/104	0.14
Positive pre-treatment culture	3/69	4/60	0.85

Cary-Blair transport media and cultured at the Naval Medical Research Unit No. 3 (NAMRU-3), Cairo, Egypt, after a maximum storage period of 5 days. Acute stool specimens from subjects with diarrhea were cultured immediately after collection in a laboratory established on the ship. Standard bacteriological methods were used to culture *Salmonella* spp., *Shigella* spp., *Yersinia enterocolitica*, *Campylobacter* spp., *Vibrio* spp., *Aeromonas hydrophila* group, and *Plesiomonas shigelloides*.

When present on the initial culture, 5 colonies of *E. coli* were selected and frozen at  $-20^{\circ}\text{C}$ . Each was assayed for heat labile (LT) and heat stable (ST) enterotoxin using commercially available DNA probes (DuPont, Wilmington, DE). Enteroadherent *E. coli* strains (EAEC) were identified by adherence to HEp-2 cells in the presence of D-mannose.<sup>12,13</sup> Slide agglutination (Bio-Merieux, France) was used to identify enteropathogenic *E. coli* strains (EPEC) and all colonies that were sorbitol negative on Sorbitol-MacConkey agar were serotyped with 0:157 anti-serum to screen for enterohemorrhagic *E. coli* (EHEC) (DIFCO Labs, Detroit, MI). All *E. coli* that were initially lysine decarboxylase negative and nonmotile were further investigated for enteroinvasiveness by the Sereny test.<sup>14</sup>

The presence of protozoa and helminthic parasites was assessed by direct microscopic examination of fresh stool and specimens prepared by merthiolate-iodine-formalin concentration (MIFC). Methanol-fixed smears were stained with a modified acid fast stain and examined for *Cryptosporidium* oocysts. Stools were also examined for rotavirus by an enzyme-linked immunosorbent assay (Rotazyme, Abbott Laboratories).

Statistical analysis was performed using SPSS/PC+ statistical package (SPSS Inc., Chicago, IL). The chi-square test with Yates correction was

used for proportions; the Student's *t*-test was used for comparison of means. Mean values were reported as  $\pm$  1 SD. Efficacy of the drug was calculated as follows: [(percent ill in placebo group - percent ill in drug group)/percent ill in placebo group]  $\times$  100.<sup>5</sup>

#### RESULTS

Initially, 262 volunteers were enrolled in the study. Of these, 20 did not return for medication, 15 withdrew prior to reaching Alexandria or took no pills, 2 transferred from the ship, 2 did not respond to attempts at follow-up, and 1 went on emergency leave, making a total of 40 volunteers who did not complete the study. A total of 222 remained for analysis.

Pre-treatment stools were submitted by 129 of the subjects completing the study. The number of these pre-treatment stools positive for enteric pathogens in the placebo and norfloxacin groups were not statistically different (3/69 vs. 4/60, respectively). Pre-Alexandria positive cultures included 5 enterotoxigenic *E. coli* (ETEC) (3-LT+, 2-LT+/ST+) and 2 EAEC. None of the subjects with positive pre-treatment stools developed diarrhea.

As noted in Tables 1 and 2, there were no differences between the placebo and norfloxacin groups in terms of age, days ashore, number of meals, or types of foods eaten. Most subjects enrolled in the study made an organized excursion to Cairo as well as day trips to Alexandria.

The frequency of compliance and side effects did not differ between the groups. Subjects in the norfloxacin and placebo groups reported missing a mean of  $0.5 \pm 1.1$  and  $0.2 \pm 0.8$  doses, respectively ( $P = 0.07$ ). Side effects were reported in 2.7% of the placebo group and 4% of the norfloxacin group ( $P = 0.9$ ). There were 2 reports

of headache and 1 report each of dizziness, urinary symptoms, constipation, nausea, and localized rash. None of these were clinically significant or required discontinuation of the medication.

Norfloxacin gave significant protection against the development of acute diarrhea. Diarrhea developed in 25.6% (30/117) of the placebo group vs. 1.9% (2/105) of the norfloxacin group (93% protective efficacy). Compliance was a problem for the 2 study subjects in the norfloxacin group who developed diarrhea. One reported a single day of diarrhea after missing a dose of medication. He did not report for follow-up at the time of his illness, but submitted a normal stool 8 days after the diarrheal episode from which no enteric pathogen was isolated. The other subject reported missing medication for 2 days prior to developing diarrhea; this subject submitted no stool specimen.

Of the 32 who developed diarrhea, 1 norfloxacin and 17 placebo subjects submitted acute stool samples. Nine of these were positive for an enteric pathogen (Table 3). The majority of isolates were either enterotoxigenic *E. coli* or *Campylobacter*. A single stool contained both *Campylobacter* and rotavirus. All of the bacterial isolates were sensitive to norfloxacin.

#### DISCUSSION

Norfloxacin was effective for the short term prophylaxis of acute diarrhea in U.S. Naval and Marine Corps personnel on shore leave in Egypt. Comparable demographic and epidemiologic data between the treatment and control groups indicate that both groups were at a similar risk of infection. The failures occurred in subjects who did not comply with the study regimen.

This study confirms findings in Mexico that norfloxacin is effective taken once daily as compared to the twice daily regimen used in Swedish travelers.<sup>10,11</sup> It also supports norfloxacin's efficacy among different study populations and in different areas of the world.

There were no serious clinical side effects. This may in part be due to the short duration of the study, although norfloxacin has been generally well tolerated even when given for up to 6 weeks for treatment of urinary tract infections.<sup>7</sup> In 2 longer prophylaxis trials with norfloxacin, side effects were minimal.<sup>10,11</sup>

TABLE 2

Comparison of exposure to diarrhea risk factors between norfloxacin and placebo groups

Factor (mean $\pm$ SD)	Placebo (n = 117)	Norfloxacin (n = 105)	P value
Meals ashore	2.8 $\pm$ 2	2.8 $\pm$ 2	0.89
Hotel meals	1.3 $\pm$ 1.4	1.2 $\pm$ 1.1	0.43
Restaurant meals	1.2 $\pm$ 1.2	1.1 $\pm$ 1.5	0.9
Street vendor meals	0.1 $\pm$ 0.5	0.1 $\pm$ 0.4	0.9
History of consuming (no. yes/total)*			
Tap water	9/117	6/105	0.75
Bottled water	86/117	72/105	0.51
Ice	31/117	30/105	0.85
Salad	26/117	28/105	0.54
Dairy products	43/116	34/104	0.59
Meat	91/117	81/105	0.97
Seafood	15/115	15/104	0.92
Dessert	52/116	50/105	0.78
Fruit	22/117	22/104	0.79
Buffet meals	60/117	53/104	0.98

\* Totals differ with no. of questionnaire responses

The antimicrobial agents doxycycline and trimethoprim-sulfamethoxazole (TMP-SMX) have undergone extensive evaluation as diarrhea prophylactic agents. Doxycycline is effective in areas where most of the isolates are sensitive, but the efficacy decreases in areas where enterotoxigenic *E. coli* are resistant.<sup>9</sup> Doxycycline resistant *E. coli* strains develop during therapy.<sup>4</sup> In addition, a recent study of U.S. Army personnel in Thailand who were taking doxycycline for malaria prophylaxis identified doxycycline-resistant *Campylobacter* as the etiologic agent in 50% of the diarrhea cases.<sup>15</sup>

Resistance to norfloxacin does not develop as rapidly as with nalidixic acid. Point mutations leading to increased MICs occur at a very low frequency, and although serial passage in the presence of the drug has lead to high-level resistance, norfloxacin inhibits the transfer of plasmids that may mediate resistance.<sup>16,17</sup> However, an isolate of *Shigella dysenteriae* with plasmid mediated resistance to nalidixic acid has been reported.<sup>18</sup> During a previous prophylaxis trial with norfloxacin, resistant bacteria were not observed.<sup>11</sup>

Antibiotic prophylaxis in this study was effective, but the question of whether to use antibiotics for prevention remains controversial.<sup>19</sup> Dietary measures are the simplest and safest methods of prevention, but it has been difficult

TABLE 3  
Etiologic agents identified in acute stool specimens of subjects with diarrhea

Organism identified	Study group	
	Placebo (n = 30)	Norfloxacina (n = 2)
ETEC	5	0
<i>Campylobacter</i>	2	0
EAEC	1	0
Rotavirus	1	0
<i>Entamoeba histolytica</i>	1	0
None	8	0
No stool submitted	13	1

to show that these measures are effective. The benefits of prophylaxis must be weighed against the potential side effects for the individual and against the global concern of emerging resistant organisms. Consequently, antibiotic prophylaxis may be appropriate only for selected populations who have a special reason to avoid developing acute diarrhea. Norfloxacin may have some advantages in terms of the spectrum of antibacterial activity, infrequent side effects, and a lower potential for development of resistant bacteria. Most individuals, however, have a rapid response to therapy when treated soon after symptoms develop, and do not require prophylaxis.

**Acknowledgments:** The authors wish to thank John McHugh, Senior Medical Officer, USS *John F. Kennedy*, for his assistance in completing this study; Isis Mikhail for *E. coli* analysis; Steven Martinez, John Williams, Tharwat Ismail, and Cecilia Callahan for technical assistance; and Nancy Scott and Jack Watkins for data entry.

**Financial support:** The Naval Medical Research and Development Command, NMC, NCR, Bethesda, MD, Work Unit No. 3M464758D849.BH.341.

**Authors' addresses:** Daniel A. Scott and Scott A. Thornton, U.S. Naval Medical Research Unit No. 3, Cairo, Egypt. Richard L. Haberberger and Kenneth C. Hyams, U.S. Naval Medical Research Institute, Bethesda, MD 20814-5055.

**Reprint Requests:** Research Publications Branch, United States Naval Medical Research Unit No. 3, FPO New York, NY 09527-1600.

#### REFERENCES

- Blaser MJ, 1986. Environmental interventions for the prevention of travelers' diarrhea. *Rev Infect Dis (Suppl 2)* 8: S142-S150.
- Steffen R, Heusser R, DuPont HL, 1986. Prevention of travelers' diarrhea by nonantibiotic drugs. *Rev Infect Dis (Suppl 2)* 8: S151-S159. UI:86261401
- DuPont HL, Ericsson CD, Johnson PC, Bitsura JM, DuPont MW, de la Cabada FJ, 1987. Prevention of travelers' diarrhea by the tablet formulation of bismuth subsalicylate. *JAMA* 257: 1347-1350. UI:87141494
- Sack RB, 1986. Antimicrobial prophylaxis of travelers' diarrhea: a selected summary. *Rev Infect Dis (Suppl 2)* 8: S160-S166. UI:86261402
- DuPont HL, Ericsson CD, Johnson PC, Cabada FJ, 1986. Antimicrobial agents in the prevention of travelers' diarrhea. *Rev Infect Dis (Suppl 2)* 8: S167-S171. UI:86261403
- O'Hare MD, Felmingham D, Ridgway GL, Gruneberg RN, 1985. The comparative in vitro activity of twelve 4-quinolone antimicrobials against enteric pathogens. *Drugs Exptl Clin Res* 11: 253-257. UI:86247050
- Wolfson JS, Hooper DC, 1988. Norfloxacin: a new targeted fluoroquinolone antimicrobial agent. *Ann Intern Med* 108: 238-251. UI: 88132128
- Mikhail IA, Hyams KC, Podgore JK, Haberberger RL, Boghdadi AM, Mansour NS, Woody JN, 1989. Microbiologic and clinical study of acute diarrhea in children in Aswan, Egypt. *Scand J Infect Dis* 21: 59-65. UI:89266672
- Sack RB, Santosham M, Froelich JL, Medina C, Orskov F, Orskov I, 1984. Doxycycline prophylaxis of travelers' diarrhea in Honduras, an area where resistance to doxycycline is common among enterotoxigenic *Escherichia coli*. *Am J Trop Med Hyg* 33: 460-466. UI:84228909
- Wistrom J, Norrby SR, Burman LG, Lundholm R, Jellheden B, Englund G, 1987. Norfloxacin versus placebo for prophylaxis against travelers' diarrhoea. *J Antimicrob Chemother* 20: 563-574. UI:88058588
- Johnson PC, Ericsson CD, Morgan DR, DuPont HL, Cabada FJ, 1986. Lack of emergence of resistant fecal flora during successful prophylaxis of travelers' diarrhea with norfloxacin. *Antimicrob Agents Chemother* 30: 671-674. UI: 87098715
- Mathewson JJ, Johnson PC, DuPont HL, Morgan DR, Thornton SA, Wood LV, Ericsson CD, 1985. A newly recognized cause of travelers' diarrhea: enteroadherent *Escherichia coli*. *J Infect Dis* 151: 471-475. UI:85132892
- Vial PA, Robins-Browne R, Lior H, Prado V, Kaper JB, Nataro JP, Maneval D, Elsayed A, Levine MM, 1988. Characterization of enteroadherent-aggregative *Escherichia coli*, a putative agent of diarrheal disease. *J Infect Dis* 158: 70-79. UI:88274113
- Silva RM, Regina FT, Trabulsi LR, 1989. Biochemical and cultural characteristics of invasive *E. coli*. *J Clin Microbiol* 11: 441-444.
- Taylor DN, Pitarangsi C, Echeverria P, Diniega BM, 1988. *Campylobacter* enteritis during dox-

- ycycline prophylaxis for malaria in Thailand. *Lancet* 2: 578-579. UI:88317914
16. Neu HC, 1988. Bacterial resistance to fluoroquinolones. *Rev Inf Dis (Suppl 1)* 10: S57-S63. UI:88159023
17. Weisser J, Wiedemann B, 1985. Elimination of plasmids by new 4-quinolones. *Antimicrob Agents Chemother* 28: 700-702. UI:86129231
18. Munshi MH, Sack DA, Haider K, Ahmed ZU, Rahaman MM, Morshed MG, 1987. Plasmid-mediated resistance to nalidixic acid in *Shigella dysenteriae* type 1. *Lancet* 2: 419-421. UI: 87313864
19. National Institutes of Health, 1986. Travelers' diarrhea: National Institutes of Health Consensus Development Conference. Bethesda, Maryland, January 28-30, 1985. *Rev Infect Dis (Suppl 2)* 8: S109-S233. UI:86261394

Accession For	
NTIS CRA&I	<input checked="" type="checkbox"/>
DTIC TAB	<input type="checkbox"/>
Unannounced	<input type="checkbox"/>
Justification .....	
By .....	
Distribution /	
Availability Codes	
Dist	Avail and/or Special
A-1	20



UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE

## REPORT DOCUMENTATION PAGE

1a REPORT SECURITY CLASSIFICATION <b>UNCLASSIFIED</b>		1b RESTRICTIVE MARKINGS	
2a SECURITY CLASSIFICATION AUTHORITY		3 DISTRIBUTION/AVAILABILITY OF REPORT <b>Approved for public release; Distribution is unlimited.</b>	
2b DECLASSIFICATION/DOWNGRADING SCHEDULE			
4 PERFORMING ORGANIZATION REPORT NUMBER(S) <b>97/89-90</b>		5 MONITORING ORGANIZATION REPORT NUMBER(S)	
6a NAME OF PERFORMING ORGANIZATION <b>U.S. Naval Medical Research Unit No. 3</b>	6b OFFICE SYMBOL (if applicable) <b>NAVMEDRSCHU THREE</b>	7a NAME OF MONITORING ORGANIZATION	
6c ADDRESS (City, State, and ZIP Code) <b>PSC 452, Box 5000 FPO, AE 09835-0007</b>		7b ADDRESS (City, State, and ZIP Code)	
8a NAME OF FUNDING/SPONSORING ORGANIZATION <b>Naval Medical Research and Development Command</b>	8b OFFICE SYMBOL (if applicable) <b>NAVMEDRSCH DEVCOM</b>	9 PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER	
8c ADDRESS (City, State, and ZIP Code) <b>National Naval Medical Center Building 1, Tower 12 Bethesda, MD 20889-5044</b>		10 SOURCE OF FUNDING NUMBERS	
		PROGRAM ELEMENT NO. <b>64758A</b>	TASK NO. <b>BH</b>
		PROJECT NO. <b>3M4647- 58D849</b>	WORK UNIT ACCESSION NO. <b>DA301562</b>
11. TITLE (Include Security Classification) <b>Norfloxacin for the Prophylaxis of Travelers' Diarrhea in U.S. Military Personnel. (UNCLASSIFIED).</b>			
12 PERSONAL AUTHOR(S) <b>Scott, Daniel A., Haberberger, Richard L., Thornton, Scott A. and Hyams, Kenneth C.*</b>			
13a TYPE OF REPORT	13b TIME COVERED FROM TO	14 DATE OF REPORT (Year, Month, Day) <b>1989</b>	15 PAGE COUNT <b>5</b>
16 SUPPLEMENTARY NOTATION <b>Published in: Am. J. Trop. Med. Hyg., 42(2):160-164, 1990; Acc. No. 1615.</b>			
17 COSATI CODES		18 SUBJECT TERMS (Continue on reverse if necessary and identify by block number)	
FIELD	GROUP	SUB GROUP	
		<b>Prophylaxis; Travelers' diarrhea; Norfloxacin; U.S. Military personnel; Alexandria, Egypt.</b>	
19 ABSTRACT (Continue on reverse if necessary and identify by block number) <b>Norfloxacin, an oral fluoroquinolone (dose 400 mg daily), was compared to a placebo in a double blinded randomized trial for the prophylaxis of travelers' diarrhea. The study was of U.S. Navy and Marine Corps personnel on shore leave in Alexandria, Egypt. A total of 222 subjects were available (105 norfloxacin, 117 placebo). In the placebo group, 26% (30/117) developed acute diarrhea vs. 2% (1/105) in the norfloxacin group. There were no significant side effects in either group.</b>  <b>* U.S. Naval Medical Research Intstitute, Bethesda, Maryland.</b>			
20 DISTRIBUTION/AVAILABILITY OF ABSTRACT <input checked="" type="checkbox"/> UNCLASSIFIED/UNLIMITED <input type="checkbox"/> SAME AS RPT <input type="checkbox"/> DTIC USERS		21. ABSTRACT SECURITY CLASSIFICATION <b>UNCLASSIFIED</b>	
22a. NAME OF RESPONSIBLE INDIVIDUAL <b>Research Publications Branch</b>		22b. TELEPHONE (Include Area Code) <b>202-284-1381</b>	22c. OFFICE SYMBOL <b>R.P.B.</b>